ITEM 6: HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SUMMARY OF LAMOTRIGINE IN SUPPORT OF THE MONOTHERAPY FOR PARTIAL SEIZURES

IN ADULT PATIENTS

1. INTRODUCTION

LAMICTAL† (lamotrigine), an antiepileptic compound of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs (AEDs). Its chemical name is 6–(2,3–dichlorophenyl)–1,2,4–triazine–3,5–diamine, its molecular formula is $C_9H_7N_5CL_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream–colored powder and has a pKa of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25 degrees C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25 degrees C). The structure formula is:

LAMICTAL is approved in the US as add—on therapy in the treatment of partial seizures in patients over 16 years of age (the original NDA 20–241 was submitted 31 December 1991). Currently, LAMICTAL is supplied for oral administration as 25 mg, 100 mg, 150 mg, and 200 mg tablets. In this supplemental NDA (sNDA), Glaxo Wellcome Inc. is requesting approval for monotherapy for partial seizures in patients over 13 years of age. Efficacy and safety data obtained in the pivotal trial US 30/31 in support of the current application are included in Item 8, Clinical Data Section. In this section, the clinical pharmacokinetics of lamotrigine in adults are reviewed, pharmacokinetics of lamotrigine in patients between 13 and 18 years of age are described and the pharmacokinetic analysis of lamotrigine performed in study US 30/31 is presented. Details about study US 30/31 can be found in the NDA Summary (Volume 1) and the final study report in Item 8, Section 8.4 of this sNDA.

2. CLINICAL PHARMACOKINETICS OF LAMOTRIGINE IN ADULTS

The pharmacokinetics of lamotrigine have been studied in patients with epileptic seizures, young and elderly healthy volunteers, and volunteers with

[†] This is a Trade Mark of Glaxo Wellcome group companies. Registered in US Patent and Trademark Office.

chronic renal failure. The following is a summary of pharmacokinetic related information in the current US Package Insert for LAMICTAL Tablets. These data were included in the original submission of NDA 20–241 (LAMICTAL Tablets; submitted 31 December 1991).

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur from hours in healthy volunteers or patients with epilepsy following single or multiple dose administration.

Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Data from *in vitro* studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to $10 \, \mu g/mL$. Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproic acid. Lamotrigine at therapeutic concentrations did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2–N–glucuronide conjugate. After oral administration of 240 mg lamotrigine to six healthy volunteers, 94% of the administered dose was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2–N–glucuronide (76%), a 5–N–glucuronide (10%), a 2–N–methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Estimates of mean apparent plasma clearance (CL/F) and plasma half-life (t½) in epileptic patients taking hepatic enzyme-inducing antiepileptic drugs (EIAEDs, including carbamazepine, phenytoin, phenobarbital and primidone), enzyme inhibitor valproate or both were 1.10, 0.28 or 0.53 mL/min/kg and 14.4, 58.8 or 27.2 hours, respectively. Therefore the elimination of lamotrigine in epileptic patients is dependent on the concomitant medication.

Following multiple doses (150 mg b.i.d.) to normal volunteers taking no other medications, lamotrigine induced its own metabolism resulting in a 25% decrease in t_½ and a 37% increase in CL/F at steady state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self induction by LAMICTAL dose not occur when LAMICTAL is given as add—on therapy in patients receiving EIAEDs.

In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg. In two small studies (n=7 and 8) of patients with epilepsy who were maintained on other antiepileptic drugs there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50 mg to 350 mg b.i.d.

Twelve volunteers with chronic renal failure (mean creatinine clearance = 13 mL/min; range and another six individuals undergoing hemodialysis were each given a single 100 mg dose of LAMICTAL. The mean plasma half–lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers. On average, approximately 20 (% of the amount of lamotrigine present in the body was eliminated during a 4–hour hemodialysis session.

In a single dose study (150 mg LAMICTAL), the pharmacokinetics of lamotrigine in twelve elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min; range were similar to those of young healthy volunteers in other studies. The clearance of lamotrigine is not affected by gender. The apparent oral clearance of lamotrigine was 25% lower in noncaucasians than Caucasians.

The interaction of lamotrigine with phenytoin, carbamazepine, and valproic acid has been studied. LAMICTAL has no appreciable effect on steady–state phenytoin and carbamazepine plasma concentration. When LAMICTAL was administered to 18 healthy volunteers receiving valproic acid (VPA), the trough steady–state VPA concentrations in plasma decreased by an average of 25% over a 3–week period, and then stabilized.

Lamotrigine is an inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications which inhibit folate metabolism.

3. PHARMACOKINETICS OF LAMOTRIGINE IN PATIENTS BETWEEN 13 AND 18 YEARS OF AGE

The pharmacokinetics of lamotrigine in adults are summarized in the previous section. A population pharmacokinetic analysis in pediatric patients with epilepsy receiving concomitant AEDs has been performed using the nonlinear mixed effect modeling (NONMEM) approach (Appendix A). The analysis included 652 steady–state plasma concentrations from 204 patients, among which 23 were in the age range of 13 to 18 years, enrolled in three lamotrigine add–on efficacy and safety trials. The estimated typical values of apparent clearance in patients at various ages receiving different concomitant AEDs are summarized in the following table.

Concomitant AEI	Appa	rent Clearance (mL/mi	n/kg)
EIAEDs	2.3 (n = 27)	6 to < 13 years	13 to 18 years
EIAEDs + VPA	0.9 (n = 5)	1.6 (n = 63) 0.6 (n = 32)	1.3 (n = 11)
VPA	0.5 (n = 19)	0.3 (n = 35)	0.5 (n = 8) 0.3 (n = 4)

Apparent clearance in patients 13 to 18 years old receiving both EIAEDs and VPA was estimated as 0.5 mL/min/kg. Mean apparent clearance of lamotrigine in adult patients taking both EIAEDs and VPA and that in adults taking lamotrigine alone are 0.53 mL/min/kg (range and 0.58 mL/min/kg (range , respectively (current US Package Insert). Apparent clearance of lamotrigine in patients between 13 and 18 years of age taking both EIAEDs and VPA (0.5 mL/min/kg) is similar to that in adults taking the same types of concomitant AEDs (0.53 mL/min/kg). It is not unreasonable to project that the clearance in patients 13 to 18 years old receiving lamotrigine alone is similar to that in adults receiving no concomitant AEDs (0.58 mL/min/kg). Therefore the apparent clearance of LTG in the absence of other AEDs in patients between 13 and 18 years of age is predicted to be approximately 0.58 mL/min/kg.

4. PHARMACOKINETIC ANALYSIS OF LAMOTRIGINE IN STUDY US 30/31

4.1 Background

The primary objective of study US 30/31 (A Multicenter, Double–Blind, Active–Control Evaluation Of The Efficacy And Safety Of Lamotrigine Monotherapy In Patients With Partial Seizures) was to compare the efficacy and safety of lamotrigine (LTG) monotherapy (500 mg/day) to valproate (VPA) monotherapy (1000 mg/day) in adult (age 13 to 73 years) outpatients with partial seizures, with or without secondarily generalized tonic–clonic seizures. Efficacy was based on the proportion of patients who discontinued treatment due to meeting one of the "escape" criteria (defined below). One of the secondary objectives of the study was to obtain LTG pharmacokinetic data during add–on treatment, during the withdrawal of concomitant liver enzyme–inducing antiepileptic drugs (EIAEDs) carbamazepine (CBZ) and phenytoin (PHT), and during LTG monotherapy.

Following screening, eligible patients entered an 8-week Baseline Phase (weeks 1 through 8) during which patients received CBZ or PHT and baseline data on seizure frequency and safety parameters were obtained. Patients then entered an 8-week Treatment Transition Phase (weeks 9 through 16) during which the study medication (either LTG and corresponding VPA placebo or VPA and corresponding LTG placebo) was gradually added to the concomitant AED over the initial four weeks and the concomitant AED was then tapered-off over the remaining four weeks. Patients who had fully

converted to monotherapy continued to receive treatment for 12 additional weeks (Monotherapy Phase, weeks 17 through 28) unless they met one of the criteria for escape (defined below) or they reported an adverse experience requiring discontinuation from the study. Patients entered the Follow–up Phase (weeks 29 through 31) following completion of the Monotherapy Phase or once conditions were met for premature discontinuation. Study medication was tapered off under double–blind conditions; treatment with concomitant AED was initiated at the same time.

Escape criteria for each patient were determined upon completion of Baseline and included evaluation of simple partial, complex partial, and secondarily generalized seizures. Patients discontinued study treatment when one of the following escape criteria were met: (1) doubling of the average monthly seizure count, (2) doubling of the highest consecutive 2–day seizure frequency, (3) emergence of a new seizure type that was more severe than the current seizure type(s), or (4) clinically significant prolongation of generalized tonic–clonic seizures. If a patient met one of the escape criteria, the dosage of the concomitant AED can be adjusted or a new AED can be added at the investigator's discretion.

A total of 156 patients, 91 females and 65 males ages 13 to 73 years, were randomized to receive LTG (n=76) or VPA (n=80). Of these, 114 patients completed the study (28 completed LTG monotherapy treatment, and 22 escaped in the LTG group; 13 completed VPA monotherapy treatment, and 51 escaped in the VPA group). A total of 26 patients in the LTG group and 16 patients in the VPA group were withdrawn during their participation in the study. Twenty (20) of these patients (14 in the LTG group and 6 in the VPA group) withdrew due to adverse experiences

4.2 Objectives

The objectives of the pharmacokinetic analysis in study US 30/31 were 1) to compare mean plasma concentrations of lamotrigine and concomitant AEDs between patients who escaped and those who remained in the study at protocol specified evaluation times; and 2) to assess the time required for plasma concentration of lamotrigine to reach a new steady–state following withdrawal of CBZ and PHT.

4.3 Methodology

Blood samples were collected at the end of weeks 8, 10, 12, 14, 16, 20, 24 and 28 to determine plasma concentrations of LTG and VPA and at end of weeks 0, 4, 8, 10, 12, 14 and 16 to determine plasma concentrations of CBZ and PHT. All samples were collected immediately prior to the next dose of medication in order to obtain trough plasma concentrations, except for week 20, 24 and 28 samples which were collected randomly throughout the dosing interval.

Plasma concentrations of lamotrigine at baseline and at the end of study weeks 10, 12, 14, and 16 (Treatment Transition) and at end of study weeks 20,

24 and 28 (Monotherapy Period) were summarized by concomitant AED (CBZ or PHT). Trough plasma concentrations of CBZ and PHT at baseline and at end of study weeks 10, 12, 14, and 16 were also summarized. For patients meeting escape criteria, plasma concentrations of lamotrigine, CBZ, and PHT recorded after their date of escape were excluded from the analysis. The concentrations of lamotrigine, CBZ, and PHT were compared between the completers and the escapers. At each assessed time point, the completer group included those who remained in the study until at least the next sampling time, and the escaper group included those who escaped between the current sampling point and the next sampling point.

Changes in lamotrigine concentrations from the end of study week 20 to the end of study weeks 24 and 28 (during the Monotherapy Period) were calculated and 95% confidence intervals were constructed. For patients meeting escape criteria, lamotrigine levels obtained after the recorded date of escape were excluded from the calculation. To ensure appropriate comparison of lamotrigine concentrations between study week 20 and study week 24 or 28, the elapsed time from dosing to sampling at these occasions were examined.

4.4 Results

Table 1 summarizes the plasma concentration of study drugs LTG and VPA during various phases of the study. Mean plasma concentrations of concomitant AEDs by visit are presented in Table 2. Plasma concentrations of study drugs and those of concomitant AEDs in completers versus escapers are presented in Table 3 and Table 4. Plasma concentration of study drugs during the Monotherapy Period of the study are summarized in Table 5 and the change in study drug concentrations at weeks 24 and 28 from week 20 are shown in Table 6. The mean elapsed time from dosing to sampling at various sampling events during monotherapy phase is compared in Table 7.

Lamotrigine concentrations were not consistently different between the completers and the escapers in patients receiving CBZ or in patients receiving PHT (Table 3). Similarly, no consistent differences in trough concentrations of CBZ or PHT were detected between the completers and the escapers (Table 4).

Mean plasma concentrations of lamotrigine increased from baseline through study week 12 during lamotrigine dose escalation (Table 1). Concentrations of lamotrigine continued to increase through study week 16 during the gradual reduction in dosage of concomitant EIAEDs. The new steady–state of lamotrigine did not appear to be reached until study week 24, 12 weeks after the dose reduction of CBZ and PHT was started and 8 weeks after the concomitant AEDs were completely withdrawn (Table 1). In the CBZ group, the median increase in lamotrigine concentration was 1.4 μ g/mL or 19% from study week 20 to week 24. The concentrations did not further increase from week 24 to week 28. The corresponding changes in the PHT group could not be precisely estimated due to the small sample size (Table 6). However, lamotrigine concentrations were slightly higher in patients who had received

CBZ compared to those who had received PHT (Table 5). The mean elapsed time from dosing to sampling was similar among study weeks 20, 24 and 28 (Table 7).

The mean trough plasma concentrations of CBZ and PHT did not change appreciably until after study week 12 when the reduction of the daily dosage of these concomitant AEDs was started (Table 2).

4.5 Discussion

In general, mean plasma concentrations of lamotrigine were comparable between the completers and the escapers at protocol specified sampling times. Similarly, no consistent differences in trough concentrations of CBZ or PHT were detected between the completers and the escapers. Therefore, patient escape from the study did not appear to be caused by lower plasma concentrations of lamotrigine and concomitant AED (CBZ or PHT).

The mean trough plasma concentrations of CBZ and PHT did not change appreciably until after study week 12 when the reduction of the daily dosage of these concomitant AEDs was initiated, indicating that the pharmacokinetics of CBZ and PHT were not affected by dose escalation of lamotrigine during the first 4 weeks of Treatment Transition.

4.6 Conclusions

Plasma concentrations of lamotrigine and concomitant AEDs carbamazepine and phenytoin were comparable between patients escaped from the study and those remained in the study. Plasma concentration of lamotrigine appeared to reach a new steady–state between 4 and 8 weeks after complete withdrawal of carbamazepine.

OVERALL CONCLUSIONS

- The pharmacokinetics information of lamotrigine in adult subjects receiving no concomitant medication is provided in the current US Package Insert for LAMICTAL Tablets;
- The apparent clearance of lamotrigine in the absence of other AEDs in patients between 13 and 18 years of age is expected to be similar to that in adults (0.58 mL/min/kg);
- 3. When patients were switched from carbamazepine monotherapy to lamotrigine monotherapy, plasma concentration of lamotrigine appeared to reach a new steady-state between 4 and 8 weeks after complete withdrawal of carbamazepine.

Project 105c-030 (Data as of: November 27, 1996)

105

Summary of Study Drug Plasma Concentrations by Visit

q6b5(030pks01) 17JAN97 12:50

LAMICTAL OF THE STATE OF THE ST

Median Min. Max. Plasma Concentration (ug/mL) 04424470 0447250 044727 23.39 23.39 23.39 53.59 ر عود عود 7.0344466 7.03644466 7.0344467 Mean 13887488 Median Min. Max. Plasma Concentration (ug/mL) 0444444 04440 044644 SD Mean 0.004420 0.006 0.0 z Study B/WK8 T/WK2 T/WK4 T/WK6 T/WK8 M/WK4 M/WK8

Post '/' indicates specific timepoint within phase.

PHASE: B=Baseline, T=Transition, M=Monotherapy, F=Follow-Up.

Page 1 of 1

	·
	1996
	6
	-
	•
	27.
	\sim
	٠.
	- 24
	•
	ñ
	7
	=
	O)
0	5
m	ħ.
×	November
Ÿ	4
•	
ΰ	
ပ္ပဲ	· ·
ည်	Ĭ.
.050	of:
105¢	of:
105c	s of: Nove
t 105c.	se of:
t 105c	as of:
sct 105c	as of:
 ect 105c-	a as of:
Ject 105c -	ta as of:
oject 105c-	ata as of:
roject 105c-	Jata as of:
roject 105c-	Data as of:
Froject 105c-	(Data as of:

		. 4	u,
		~	4
		- ('n
		~	٠.
			>
		•	
		١,	
		- 7	ς,
		-	4
		. 0	?
		2	•
		C	٠.
			ł
		1	١.
		π	1
		S.	
		ü	
		~	е,
		-	
		71	
		×	
		*	
		ņ	
		O	
		ℼ	
•	A	Ε	
		Ø	
-	Φ	æ	
,	ù.		
		⊸	
	57	7	
4	ą,	7	
9	G G	TA C	
Ë	de l	I A	
Ë	1 400	TA CAN	
Ë	1 400	AED PL	
Ė	Tabl	AED PL	
E	100	C AED PL	
E	TAD.	IIC AED PL	
E	Tabl	auc AED PI	
E	Tan I and	cant AED PI	
Ė	trant and	TA UTH AED BI	
J. E	TAD	"LECALL AED PI	
E	TADI	omitain AED PI	
E	Labi	-outeant AED PI	
E		COULTAIN AED PI	
J. E	Lab.	STECHILL AED PI	
J. E		Some Calle AED PI	11/1 cm
J GE	Concomitent and Lab	CONCOMITCAIL AED PI	
J S E	CONCORTENT TOTAL	Correcting AED PI	7 3 1/4 (2000 - 2
E	of Concomitant and Concomitant	- correcult and PI	7 2 1/4 Comp. 2
E	of Concomitant and Lab	- correquireant AED PI	7 2 37 4 7000 2 2
J. E	Concomitant and	- correquireant AED PI	7 2 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4
J. E	V of Concomitent and	TA CATACAMT CAME AED LI	
1 4 E	ITY OF CONCOMITORS SEE TABLE	Id O'AR O'MITCAME AED DI	
J. E	lary of Concomitent and	- concountain AED PI	
J. E	mary of Concomitent and	TA CANCOUNT CALL AED PI	
JeE	mmary of Concomitent and	Id (TAK) IIIT AED LI	
J. E	unmary of Concomitant IdDIe 2	Id (TAK) IIIT CAIRC WED LI	A 2004 CA A
J. E.	Summary of Concomitors and	I CATECOUNT CAUL AED FI	
I E	Summary of Concomitent and	TA CATTCALL AED LI	
T CE	Summary of Concontract and	I CONCOMITCAIL AED PI	
1 °E	Summary of Concomitant and	TA CAMPANIT ARD LA	
1.4E	Summary of Concomitant and	Id (TAK) III CONTROLLING WED LIT	
1,48	Summary of Concomitent and	Id (IAK) III CONTROLL ARD L	
1.4E	Summary of Concomiter , and	Id (IAK) III Called AED DI	
J. E	Summary of Concomitent and	Id Old Trading AED DI	
J.E	Summary of Concomitant and	Id (Tay) intraville AED bI	
T.E.	Summary of Concomitant and	Commodition AED Plasma Concentrations by Will	

q6b5(0301ds04) 17JAN97 12:50

			:	X
		(nd/mr)	× × ×	
TIDA COTT	S GROOP	Flasma Concentration	Median	2000 88 8 8 1 1 4 4 1 1 1 4 4 1 1 1 1 1 1 1
(0,1)		Concer	SD	4488444 0004480W
		Flasma	Mean	0000000 000000000000000000000000000000
	-		z	4844484 80884441 00841108 48889844
		!	Max.	
e de	(na/mr)		- MIM 1	
ICTAL GROUP	Concentration	Modified	į.	С. С
LAM	Plasma Con	Mean SD		0008570. 7.00080. 7.0000. 8.00080. 8.000.
	P1			222222 2444 2522222 24112 100 110 12112 12112 120 120 120 120
	Study	Week		0480040 0480040
		Phase		B/WK9 B/WK4 B/WK8 B/WK8 T/WK8 T/WK6 T/WK8 B/WK8 T/WK2 T/WK2 T/WK2 T/WK8
		AED		CBZ

Some service of the control of the c

PHASE: B=Baseline, T=Transition. Post '/' indicates specific timepoint within phase.

		į	0	ř., i	
		Ų	0		
			0		
		0	0		
		9	0		
		0	2		
		000	0		
		1000	0 6 6 7		
		100	200		
		100	2000		
		1000	OKCT .		
		1001	0667		
		1000	1000		
		7 1006	0000		
		1006	0000		
		7006	0000		
		27 1006	DECT TORE		
		27 1006	1000		
		27 1006	0000		
		7 7 1006	0000		
		r 27 1006	0000		
		3r 27 1006	0000		
		ar 27 1006	0007 117		
		2001 7C 70C	0007 113		
		her 27 1006	0667 117		
		her 27 1006	0667 117		
		mber 27 1006	0007 112		
		mber 27 1006	0000		
		ember 27 1006	0667 177		
		Tember 27 1006	0000		
	0	Vember 27 1006	0667 177		
	0_	Vember 27 1006	0667 113		
	30	OVember 27 1000	0007 177		
	30	Ovember 27 1006			
	030	November 27 1006	0007 177		
	-030	November 27 1005	0667 177		
	-030	November 27 1006	0667 177		
	-030	November 27 1006			
	2-030	November 27 1006			
	G-030	November 27 1006	0667 177		
	oc-030	: November 27 100c	0667 177		
	5c-030	f: November 27 100c	0667 177		
	150-030	f: November 27 100c	066T 117 TOWN		
	056-030	of: November 27 1000	0667 177 1030		
	.056-030	of: November 27 1006	12 TO		
	1056-030	of: November 27 1000	12 TO		
	1050-030	of: November 27 1000	1230		
	1056-030	3 of: November 27 100c	1330 TA		
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1050-030	S of: November 27 1005	0 F T 1 7 T T T T T T T T T T T T T T T T T		
	c 105c-030	as of: November 27 100c	066T 117 TO		
	C 105G-030	as of: November 27 1000	066T 177 TO		
	cc 105c-030	as of: November 27 100c	066T 117 TO		
	GC T02G-030	as of: November 27 1000	066T 117 TO		
	3cc 105c-030	as of: November 27 100c	066T 117 TO		
	ecc 105c-030	a as of: November 27 100c	DCCT 1/7 TOC		
	180c 1050-030	a as of: November 27 100c	06CT 117 TO		
	Jecc 105c-030	ta as of: November 27 100c	066T 117 TOWN		
	Ject 105c-030	tta as of: November 27 100c	06CT 117 TOWN		
	0)ecc 1026-030	ata as of: November 27 100c	066T 1/7 TO		
	olect 105c-030	ata as of: November 27 100c	06CT 1/7 TOWN		
	To) ecc 1020-030	Data as of: November 27 100c	7330		
7 1 1 7 3	Tolect 105c-030	Data as of: November 27 100c	10 T 117 T 1230		
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	103ecc 1020-030	(Data as of: November 27 100c	1230 TO		
	Fig. 1050-030	(Data as of: November 27 1006)	1230 T		

				i		LAM	LAMICTAL				2727				
Phase St	Study	Efficacy	Baseline AED	2	Plasma		Concentration	(ng/mr)			Plasma		Concentration	(12/2011)	
B/Wkg				:	real!	202 	Median	Min.	Max.	z	Mean	SD	Median	i .	
	* 0	Completer	All CBZ PHT	4727 7257	000	000	000			47	40		0.0	100	Max.
T/Wk2 1	10	Completer	All CBZ PHT	0.87	27.		9 41	the half of transfer delicate transfer as a	o Mandro Maria Na Amerika da Santa da Panga da P	18 49	1.1	24 W	0.0 R	Accommodate to the second	i formeser rocker ty franco seem skall.
T/Wk4 12		Completer	A11) Q	•	•		n El terrenne <u>nt enne</u>	endenty old a laboratory	79 103	41.8	18.5	38.5	no have same again the log	and the same of the same of the
		Escaper	CBZ PHT	124 1440			24.4 24.0			51 17	49.6 51.1 46.5	20.3	446.00 20.00	1969 sülde en einstaleide kanne.	ate dans di anno a da segui
			CBZ	0 44	4.w.r. e.r.e.	w04 w00	www 7.7.9		Anna Carlotte Commission Commissi	LW4	288.3 288.3			Service Service	
		Completer	All CBZ PHT	1334	ARW QuH	7.01 1.01	444 000		No. of Samuel Control of Samuel	32	min				in the hard of great participation is a second
	N	Escaper	All CBZ PHT	യനഗ	41.7					0 10 10	ω N.		32.5		economic destinations
T/Wk8 16		Completer	All CBZ PHT	182 185	η. 10.4π			arters do tara d			0 1		66. 64. 66. 7		
	ជ័	Escaper								0,00 =100 1360 =4460	4,0 0 8 Vii 0 4	115.8 112.28 26.8	35.24 35.94 40.40		
M/Wk4 20	8 ,	Completer	All 28 CBZ 21 PHT 7		7.8	640 040	7.7. 2.6.0			4 66	o	o 00	.4. C.		
	ม	Escaper	A11 C	0				Property.			H	3.7	10		

PHASE: B=Baseline, T=Transition, M=Monotherapy, F=Follow-Up. Post '/' indicates specific timepoint within phase.

		1996)
		27,
	30	Н
1	0-050T 1:	as of: Novembe
Paris C	Second Second	(Data as

٠.			
	٠,	ű	
		Ø	
		>	•
	•	コ	
		ä	
		₹	
		Ĵ	
		ú	
		=	
	- 1	ų.	
	4	٠,	
	C	Ω.	
	ž	ì.	
		ŀ	
	9	?	
	- 7	1	
	÷	ŧ	
	-	•	
	۳,		
	Ω		
	C	ļ.	
3	a		
m	ပ္က		
·	~		
_	O		
P	ပိ		
apl	ပ္ပ		
Tabl	na Co		
Tab1	sma Co		
Table 3	asma Co		
Tabl	lasma Co		
Tabl	Plasma Co		
Tabl	g Plasma Co		
Tabl	ug Plasma Co		
Tabl	orug Plasma Co		
Tabl	Drug Plasma Co		
Tabl	Y Drug Plasma Co		
Tabl	luy urug Plasma Co		
Tabl	-udy Drug Plasma Co		
Tabl	Scual Drug Plasma Co		
Chind: F. Tabl	Schol Drug Plasma Co		
Tabl	ocady Drug Plasma Co		
Of China: F. Tabl	or sendy Drug Plasma Co		
Tabl	1 of Study Drug Plasma Co		
Tabl			
nary of child. F. Tabl	or sendy Drug Plasma Co		
mmary of study, but	The seady Drug Plasma Co		
ummary of study, p. Tabl	or sendy Drug Plasma Co		
Summary of study, by Tabl	The send brug Plasma Co		
Summary of study, but	Drug Plasma Co		
Summary of study, but	The search brug Plasma Co		
Summary of chinds has Tabl	The search Drug Plasma Co		
Summary of childs Free Tabl	Journal Drug Plasma Concentrations hy grant		

q6b5 (030pks03) 17JAN97 12;51

			Max.					
		(nd/mr)	Min.		and the same and t	To the Desire of State of Stat		According to the second section.
	VPA	Plasma Concentration (ug/ml)	Median Min.	63.7	67.7	61.1 74.1		67.99 9.49 9.49
		Concen	SD	64.0 23.3	19.0	10.3		227 280.13 20.13
STS/THURS		Plasma	Mean		68 4.0	71.5	72.3	78.0 65.2
	-		z	v	17.00)4 O	> 6	W4 OC
	130/101	(7)	Min. Max.					
LAMICTAL	Plasma Concentration (110/mr)	Model	"edian		ຜູຍ ເ ເນເນເ	10.1	ر. ون	00 00 00 1010
LAN	Concen	GS.			44.) ,	w	.c.
	Plasma	Mean			10.3	10.1	∞ σ	6.0 6.5 5.5
-				>	50.9 80.9	ਜਜ	112	∜ ਜਜ
		AED		7000	All CBZ PHT	All CBZ	A11 CBZ	All CBZ
	Study	Efficacy	Escaper		Completer	Escaper	28 Completer	Езсарег
	Study	меек	20				28	7

PHASE: B=Baseline, T=Transition, M=Monotherapy, F=Follow-Up. Post '/' indicates specific timepoint within phase. Section of the sectio

Page 2 of 2

RM1997/00402/00

M/Wk4 Phase

M/Wk8

M/Wk12

11

105

Project 105c-030 (Data as of: November 27, 1996)

Summary of Concomitant AED Plasma Concentrations by Visit and Efficacy Response

q6b5(0301ds08) 17JAN97 12:50

	AED	fficacy N Mean	ALL Completer 30 9	ALL 23 9 Completer 23 9	ALL 29 8. Completer 29 8.	ALL 29 8. Completer 29 8.	ALL 28 7. Completer 26 7. Escaper 2 10.	ALL 27 5. Completer 23 5. Escaper 4 5.	ALL 22 3. Completer 21 3. Escaper 1 1.	ALL 20 17.4 Completer 20 17.4	ALL Completer 17 19.	ALL Completer 19 19:	19 21. 19 21.	ALL 19 18.5 Completer 15 18.3 Escaper 4 19.0	16 8.8
LAMIC	lasma Conc	n SD	.1. 2.8 2.8	.6 2.6 2.6	6. 8.0	2.2	9.79		0.40 HH 8.8	4 7.0	44.	3 7.2	2 8.7	5 7.2 6.4 10.7	5.2
LAMICTAL GROUP	Plasma Concentration (ug/mL)	Median Min.	9.0	00	7.9	00	7.4 4.7 6.0	ww.4	мм-т Ощо Ощо	17.0	00.0	18.0 18.0	20.0 20.0	20.00 0.00 0.00	بن ش
	(,	Max.			Market - wasana	ozoro toto fizicani	www.no.com.com.com.com.com.com.com.com.com.co		sa kunna a tilipiatin yasing			. 70	100	703	19
	1	N Mean	39 99 9.1	25 25 9.8	88 66	35 35 8.4	347 347 3888 522	31 7.1 220 6.9 11 7.3	04.0 6.04.0 6.04.0	111 19.6			21 14.5 21 14.5	mma	9
VPA GROUP	Plasma Concentration (ug/mL)	SD Med	2.2	ເບັດ	, vov	0 10	N MM M	1 0000	i un⊣ , mmm	88.7 7.117.	1 6			 www	5 .5
an.	ation (ug/	Median Min.		ı vç	, w.	· ••	່ ເນື່ອວ	HMC	, 404	o.				o on	
	mL)	Max.			Policina de managad	atronamenta and	The state of the s	one and the second second second		1 1	erinanga Sarah		Abstracts success		· · · · · · · · · · · · · · · · · · ·

PHASE: B=Baseline, T=Transition. Post '/' indicates specific timepoint within phase.

Project 105c-030 (Data as of: November 27, 1996)

q6b5(0301ds08) 17JAN97 12:50 Summary of Concomitant AED Plasma Concentrations by Visit and Efficacy Response

	AED Plasma Concentration (ug/mL)	Completer 11 8.4 6.0 8.0 12 6.4 5.4 4.0 ALL Completer 7 2.5 2.0 1.5 1.5 1.5 1.5 Escaper 1 1.5 2.1 1.5 1.5 1.5 1.5
APP PI	N Mean SD Median Min	Completer 11 8.4 6.0 8.0 ALL Scaper 5 9.6 3.2 10.0 Completer 7 2.5 2.0 1.5 Escaper 1 1.5 2.1 1.5
	Study	/Wk6 14 /Wk8 16
		16

13

PHASE: B=Baseline, T=Transition. Post '/' indicates specific timepoint within phase.

Project 105c-030 (Data as of: November 27, 1996)

q6b5(030pks06) 17JAN97 12:51

Plasma Concentration of Study Drug During Monotherapy Period LAMICTAL

	1									
			Max	ļ	g saweiz		er can e e e		والمعادية المرازين	
	g		Min	www.doc.doc/eclose	and the state of	er torday	ed vice volume			
VPA	Plasma	(ng/mr)	Median	70.8	5.0.0	6.7.9	72.1	6.79	61.8	69.4
	Con		SD	20.3	18.2	60.0	22.6	20.1	19.3	28.6
			nean	67.4	72.3	?	68 66.8	78.0	65.3 71.6	65.2
1		2	1	86	76		172	Ŋ	95	4
		Max			***	\$200 Q.O.	E) to school to 1		o o o o o o o o o o o o o o o o o o o	
	s	Min				and the section				
Dlacma	Concentration (ug/mL)	Median		. 8 . 9	7.9		, σ. α		- wc	;
	Conc	SD		5.7 5.7	8	0.4	ωω Γ.Γ.		,00 ,00	
		Mean		10.1	7.30	8.2	11. 9.51	7.1		
		Z	¥	781 181	0	23	122	00	64	
	Study	Week	ç	777	0	50	77 78 8	20	22 28 48	
		AED FRASE	M/Wk4	M/WK8 M/WK12		M/WK4	M/Wk12	M/Wk4	M/WK8 M/WK12	
	6	dar.	A11			797		PHT		

14

PHASE: M=Monotherapy. Post '/' indicates specific timepoint within phase.

		-	
			٠.
			О
			Ξ
		•	v
			200
		•	
		- 1	
		τ	•
		•	7
		•	•
		- 4	٠.
		- 4	ч
		- 1	31
		- 2	Ξ
		,	4
			=
			•
		•	ν
	٦		Š
- 3	_		-
۲	7	•)
•	٦	-	•
-	•	-	٠
	J		
	'n		
_ `	¥		7
ш	п	ų.	ŧ
•	٠.	_	ċ.
٠	•	•	,
•	4		
			ı.
	2	v.	
1	,	a	
	١.		
•	,		
0	ď	~	
_	Ξ.	: 4	
•	7	·	
c	١.	at	
÷	٠.	۳	
٠	4 1	-	
α		Data as of Moromban	
	•		

105

						۱
					1	١
					ŧ	
					•	
					٩	į
					1	ĺ
					ì	
					•	
				4	r	
					١	
					r	
					č	
				•	_	,
					Ľ	١
					Y	
				٠	S	
٠		į	į.	4	_	
١	ų	U	,	4	τ	
	(ľ	ľ	5		
	(2		
	0			2	110,10	
		1		200	110,770	
		1		2011	1077	
		1		7727	101001	
		1		アイカイナー	10.100.	
		1		サール アートラング	110 10 10 10	
	-	1		1011111111111111111111111111111111111	10.100	
E	(1		TO THE PLANT OF THE PARTY OF TH	TOTO BY	
T. T. E.	(1		CONTRACTOR AND THE COLOR	101000000000000000000000000000000000000	
	(1			TO 5 40 10 10 10 10 10 10 10 10 10 10 10 10 10	
	0	H TOPY		COLUMNITATION	77777	
E	0	H TOBY		TAT LEGUIDO		
 E	0	H TOBY		TATE COLOCAL STREET		
	0	H TODY	111111111111111111111111111111111111111		IIC TO B TOTAL	
	0	HTCD*	1	TO THE PROPERTY OF THE PARTY OF	TOTO TOTO	
 T TE	0	HITCH	100 000	TOTAL CONTRACTOR STATE	TOTO BYOUR O	
	C	# TOBY	11.00	TOTAL CONCENTION OF	TOTO TOTO	
	C	#TODY	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	TOTAL CONCENTION	TOTO BY TOTO	
	C C C	# TODY		TOTAL CONCENTINATION	TOTO TOTO CO.	
	C C C	H 100	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	TO THE COUNTY TO THE	TOTO TOTO	
	C 1	+ + + + + + + + + + + + + + + + + + +		TOTAL CONCENTION OF THE	TOTOR TOTOR	
	C C C C C C C C C C	# TODY	THE PARTY OF THE P	TOTAL CONCENTION OF	IIC TO B TO TO CO.	
	C	# TO T	THE PARTY OF THE P	TOTAL CONCENTION OF	TOTOB TOTO	
	C	# TO 5	The state of the s	TOTAL CONCENTION OF		
	C	1 TO	THE PROPERTY OF THE PARTY OF THE	TOTAL CONTRACTOR		
	C C C C	1 TO	THE STATE OF THE STATE OF THE	TOTAL CONCENTION	TO TO B TO TO TO	
	CIT	1 TO	THE POLICE AND THE DESCRIPTION OF THE DESCRIPTION O	TOTAL CONCENTION	TOTO BYOLD	
	C C C C	1 TO	THE PARTY OF THE PARTY OF	TOTAL CONCENTION	TOTO PARTICION O	
	C C C C C C C C C C C C C C C C C C C		THE PARTY OF THE PARTY	TO THE COUCHE TO THE TABLE OF		
	C C C C C C C C C C C C C C C C C C C		THE PROPERTY OF THE PARTY	TOTAL CONCENTION		
	C C C C C C C C C C C C C C C C C C C		THE PROPERTY OF THE PROPERTY O	TOTAL CONCENTION	TOTOB TOTO	
	C C C C C C C C C C C C C C C C C C C		THE DESIGNATION OF THE DESIGNATION OF THE PERSON OF THE PE	TOTAL CONCENTRAL		•
			THE PROPERTY OF THE PROPERTY O	CONCENTRAL CONCENTRAL OF THE PROPERTY OF THE P		

q6b5 (030pks04) 17JAN97 12:51

The state of the s	VPA	Plasma Concentration from Week 20 Percent Change (%) Absolute Ch.	11 9.8 (-10.1,24.8) 3.8 (-9.1,14.1) 5 3.0 (-21.8,18.1) -0.1 (-15.2,14.1) 5 24.8 (-13.6,50.4) -0.5 (-15.2,14.1) 5 24.8 (-13.6,50.4) -1.8 (-15.2,14.1) 7 (-21.2,13.1) -0.1 (-15.2,14.1) 7 (-13.2,13.1) -0.1 (-15.2,14.1) 7 (-13.6,50.4) -1.8 (-14.7,10.7)
LAMICTAL	Plasma Concentration from Work 20	Percent Change (%) Absolute Change (ug/ml) N Median 95% CI Median 95% CI	27 10.5 (2.7,33.1)* 1.0 (0.2,2.4)* 1.2 (0.2,2.4)* 1.2 (-0.8,1.8) 1.3 (-0.4,2.4)* 1.4 (-0.6,3.0)* 1.5 (-1.0,2.3) 1.5 (-56.3,135.6) 1.6 (-3.7,2.4)
		Study Week	22 22 22 28 48 48 20 21 12
		AED Phase	ALL M/WK8 M/WK12 CBZ M/WK8 M/WK12 PHT M/WK8

Analysis is restricted to observations with corresponding Week 20 value. PHASE: M=Monotherapy. Post '/' indicates specific timepoint within phase.

'*' indicates significance of p <= 0.05.

Project 105c-030 (Data as of: November 27 1006)
030 November 27 1006)
-030 November 27 1006)
-030 November 27 1006)
030 November 27 1006
030 November 27 10060
-030 November 27 1006)
030 November 27 1006)
030 November 27 10061
030 November 27 10060
030 November 27 1006)
030 November 27 1006)
030 November 27 10061
030 November 27 10060
030 November 27 1006)
030 November 27 1006
030 November 27 10060
030 November 27 1006)
030 November 27 1006)
030 November 27 10061
030 November 27 10063
030 November 27 1006)
030 November 27 1006)
030 November 27 10060
030 November 27 1006)
2-030 November 27 1006)
030 November 27 1006
030 November 27 10060
030 November 27 1006)
2-030 November 27 1006)
030 November 27 1006)
030 November 27 1006)
2-030 November 27 1006)
2-030 November 27 10060
2-030 November 27 1006)
2-030 November 27 1006
2-030 November 27 100
2-030 November 27 100
2-030 November 27 10
2-030 November 27 10
2-030 November 27 1
2-030 November 27
2-030 November 2
2-030 November
2-030 November
2-030 November
2-030 November
2-030 Novembe
2-030 : Novembe
2-030 Novemb
2-030 : Novem
2-030 Novem
2-030 1 Nove:
2-030 Nove
2-030 Nov
2-03(Nox
2-03 No
ož
02
1
[]
மை
- 0
m
- D &
U
<u>ر</u>
9 4
9 8
ည် အ ရ
oje ta
ojec Jata
rojec Data
Projec (Data
Projec (Data

	N	1			
	S				
Ť,	N				
	⊣ i				
	-				
	5				
	3				
	7				
	[]				
	٠,				
	_				
	6				
	Ŋ				
	á				
	σ.				
. :	Ξ.				
	\simeq				
. 1	Š				
٠,	Ğ.,				
	ס.				
					. 1
				. 1	ا
				- 6	
				5	- 1
					!
					í
					Í
					ď
			Φ		į
		٠.	σ.		ł
			Ę		i
		,	σ.		!
		•			i
		7	<		ļ
		٠	4		-
		. (5		ij,
		. •			1
			D .		i:
			2		
		_ C	₽.,		1
		_ C) }		!
	ı	- tu))		1111
	ı	ر المرد. ال)) (1
	į	ון אפר / היד אפר)))		1
	į	Die / Pr Last D)		
		Table / ter Last n	3		
		rable / Eter Last n	3		
	į	after Last n	1		
	į	Table / e after Last n	3		
		Table / ime after Last n	3		
	Ē	Time after Last n	1		
	E	Time after Last n			
	Ē	of Time after Last n		AL	
	Ē	of Time after Last n		TAL	
	E	ry of Time after Last n		ICTAL	
	E	lary of Time after Last n		MICTAL	from Took District
	E	mmary of Time after Last n		LAMICTAL	2 fx0m 102h X
		Jummary of Time after Last n		LAMICTAL	TO FYOM TOWN THE PARTY OF
		Summary of Time after Last n		LAMICTAL	PARO From I and Date
		Summary of Time after Last n	Service Control of the Control of th	LAMICTAL	THE FROM LOSE TO
		Summary of Time after Last n		LAMICTAL	mino from Took D
		Summary of Time after Last n		LAMICTAL	Pino from Took D
		Summary of Time after Last n		LAMICTAL	T-10 FYOR TOOL D.
		Summary of Time after Last		LAMICTAL	man from 100 to
		Summary of Time after Last			# # 100 From 1001 P
		Summary of Time after Last n			11-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1
		Summary of Time after Last n			# # # # # # # # # # # # # # # # # # #
		Summary of Time after Last n			mag from 1001
		Summary of Time after Last n			T-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1
1966		Summary of Time after Last n			# # # # # # # # # # # # # # # # # # #
19861		Summary of Time after Last n			## ## ## ## ## ## ## ## ## ## ## ## ##
1996)		Summary of Time after Last n			(1) E
77, 1996)		Summary of Time after last n			(1) (1) (1) (1) (1) (1) (1) (1) (1) (1)
27, 1996)		Summary of Time after Last n			11111111111111111111111111111111111111
r 27, 1996)		Summary of Time after Last n			11111111111111111111111111111111111111
ber 27, 1996)		Summary of Time after Last n			
mber 27, 1996)		Summary of Time after Last n			
/ember 27, 1996)		Summary of Time after Last n			
Ovember 27, 1996)		Summary of Time after Last n			
November 27, 1996)	G655 (030pks07) 173AN97 12:52	Summary of Time after Lact now to my			m*mo from 100 fr

Commence of the commence of th	Time from Last Dose to PK Sample (h)	Mean SD Median Min Max	6.4.7.0 0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0	
		Max N Mear	18 13 7.0 9 6.0	
TWINTER	Time from Last Dose to PK Sample (h)	Mean	31 8.1 6.2 5.8 16 6.5 3.9 5.1	
	Study Phase Week	i	M/Wk8 24 M/Wk12 28	

16

PHASE: M=Monotherapy. Post '/' indicates specific timepoint within phase,